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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/393,579	09/09/1999	STEVE DE KECZER	IR98-7410	2931

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EXAMINER
CELSA, BENNETT M

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 12/19/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

file copy

Office Action Summary

Application No.	Applicant(s)
09/393,579	De Keczer et al.
Examiner	**Art Unit**
Bennett Celsa	1639

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Oct 15, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-45 and 47-56* is/are pending in the application.

4a) Of the above, claim(s) *2-13, 17, 18, 20, 31, 34-36, 45, and 47-56* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 14-16, 19, 21-30, 32, 33, and 37-44* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/15/02 has been entered.

2. **NOTE**: the location of the present application is now **ART UNIT 1639.**

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of the Claims

Claims 1-45 and 47-56 are currently pending.

Claims 2-13, 17-18, 20, 31, 34-36, 45 and 47-56 are withdrawn from further consideration.

Claims 1, 14-16, 19, 21-30, 32, 33 and 37-44 are under consideration. .

Election/Restriction

4. Applicant's election without traverse of Group III (claims 14-16, 19-30, 32-44 and 46) in Paper No. 5 is again acknowledged.

5. Applicant's further election of species , in Paper No.5 of :

a. *α-bromoacetylbenzoic acid (BABA) as the "protected alkylating agent".*

b. phosphine as the "disulfide reducing agent";

c. alkaline phosphatase as the "activating agent capable of deprotecting to the protected alkylating agent"; and

d. an antibody as the "reagent capable of specifically binding to modified homocysteine", is acknowledged, which reads on claims 1, 14-16, 19, 21-30, 32, 33, 37-44 and 46. Because applicant did not distinctly and specifically point out the supposed errors in the election of species requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)) . It is noted that the sake of expediency and compact prosecution, claim 1 was included in the elected invention since claim 14 is dependent thereon.

Withdrawn Objection (s) and/or Rejection(s)

Applicant's amendment has overcome the previous new matter rejection of claims 1, 14-16, 19, 21-30, 32, 33 and 37-44.

Applicant's amendment has overcome the indefinite rejection of claims 19, 21-30, 32, 33 and 37-44 of term *"capable of reacting* with a functional nucleophilic group" and "*unreactive* to a nucleophilic group".

Applicant's amendment has overcome the previous indefinite rejection of claims 1, 15,16,19, 32 and 44 due to the terms "a protected alkylating agent" and "chemically modifying homocysteine"

NEW (OR REVISED) ***Objection (s) and/or Rejection (s)***

Claim Rejections - 35 USC § 112

6. Claims 1, 14-16, 19, 21-30, 32, 33 and 37-44 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (NEW MATTER REJECTION).

Applicant's amendment (e.g. of claims 1, 19, 32 and 44 and claims dependent thereon) referring to derivatizing haloketones and haloaldehydes and the properties of the protecting group (e.g. "renders alkylating agent.. on the protected functional group") which are not present in the specification or original claims and to which no specification support was pointed to constitutes new matter. Applicant must cancel the new matter in response to this rejection.

Claim Rejections - 35 USC § 112

7. Claims 1, 14-16, 19, 21-30, 32, 33 and 37-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 1, 19, 32 and 44 (and claims dependent thereon) are confusing as to whether an alkylating reagent is a haloketone or alpha haloaldehyde or some derivative thereof since the preamble of the claim addresses an alkylating reagent comprising a haloketone/haloaldeyde whereas the latter portion of the claim contains process limitations (e.g. derivatizing).

Accordingly, if a product-by -process is desired, the claim should be amended to more clearly recite the same(e.g. a protected alkylating agent produced by the following process ...).

B. In claims 1, 19, 32 and 44 (and claims dependent thereon), use of the terminology "having a haloketone or alpha haloaldehyde functional group" is indefinite as to what part of the alkylating agent constitutes the functional group e.g. the whole haloketone (or haloaldehyde)? the halogen? the carbonyl?.

C. In claims 1, 19, 32 and 44 (and claims dependent thereon), use of the term "said alkylating agent having its haloketone or alpha haloaldehyde functional group derivatized with a protected functional group" is indefinite as to what portion of the alkylating agent is being derivatized; and the metes and bounds of "functional group derivations" within the scope of the claim; and the resulting final structure of the derivatized functional groups of the alkylating agent.

D. The amendment of claim 1(and dependent claims) to recite both reactivity and nonreactivity to a nucleophilic or sulfhydryl group under biological conditions of the alkylating reagent is indefinite.

E. In claim 1 (and dependent claims) use of the term "nucleophilic or sulfhydryl group" is confusing since a sulfhydryl group can (and often does) function nucleophilic (e.g. in the presence of an electrophile).

F. Claim 1 (and dependent claims) lacks metes and bounds regarding the types of reactions to which the alkylating reagent is susceptible in the presence of a nucleophile (or sulfhydryl group) and an enzyme.

8. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated or in the alternative as prima facie obvious over CAPLUS AN 1991:631804 to Schepin et al. Zhurnal Organicheskoi Khimii (1990) Vol. 26(11) pages 2394-7 (and RN 13654-49-4 and RN 136454-32-5) alone or if necessary further in view of the specification to demonstrate inherency.

Amended claim 1 can be interpreted as a **product-by -process** claim drawn to "an alkylating agent" made by reacting an "haloketone or alphahaloaldehyde" containing a functional group (e.g. a carbonyl) with a "protected functional group" (e.g. derivatized); the resulting protected functional group (e.g. a carbonyl protecting group) resulting in the claimed degree of activity when exposed to an enzyme and a nucleophile or sulfhydryl group.

The Schepin Abstract discloses compounds (e.g. see RN 13654-49-4 and RN 136454-32-5) which are "Protected haloketone" alkylating compounds within the scope of the present invention as described in the present specification and formula (e.g. see specification page 9, lines 20-25); wherein the reference compounds have an ester protecting groups. The reference compounds are thus "protected haloketone" alkylating compounds within the presently claimed invention in light of applicant's own specification teaching and thus must satisfy the new limitations regarding derivation and reactivity as summarized in the above paragraph.

9. Claims 1 and 14 are rejected under 35 U.S.C. 102(b,e) as being anticipated or in the alternative as prima facie obvious over Metzger et al. US Pat. No. 5,700,910 (12/97) alone and if necessary further in view of Morrison & Boyd Organic Chemistry 3rd ed. 1973 pages 562-563 and CAPLUS Abstract No. 1947:25587 to Bergkvist, T. Svensk Kem. Tid. (1947) Vol. 59 pages 24-27 to demonstrate properties inherent in the Metzger et al. compound or its manufacture..

Amended claim 1 can be interpreted as a **product-by -process** claim drawn to "an alkylating agent" made by reacting an "haloketone or alphahaloaldehyde" containing a functional group (e.g. a carbonyl) with a "protected functional group" (e.g. derivatized); the resulting protected functional group (e.g. a carbonyl protecting group) resulting in the claimed degree of activity when exposed to an an enzyme and a nucleophile or sulfhydryl group.

It is noted, that a product-by process claim is deemed by the PTO as a product claim; wherein the process claim limitations are not afforded patentable weight.

Metzger et al. disclose a composition comprising a "disulfide reducing agent" (e.g. Zn in HCL/H2SO4: see col. 2, lin 41) and a "protected alkylating agent" of formula III (e.g. an epoxide see col. 2, line 45) which anticipates the presently claimed invention.

Additionally, the Metzger et al. Epoxide alkylating agent is capable of being made from a halohydrin (e.g. see Morrison & Boyd page 562 "Preparation of Epoxides") which halohydrin can be made from the reduction of a ketone or aldehyde (e.g. see CAPLUS Abstract). Thus, the Metzger et al. Epoxide alkylating agent can be produced through the derivitization of a

haloketone or haloaldehyde whose functional group (e.g. carbonyl) is protected by the formation of an epoxide group.

The ability of the protected carbonyl (e.g. epoxide) to possess the requisite degree of reactivity under biological conditions to a nucleophilic or sulfhydryl group in the presence of an enzyme is a characteristic which is inherent to the reference compound which meets all the other material chemical and functional characteristics as presently claimed. In this regard it is additionally noted that the Metzger formula III composition would be within the scope of the presently claimed invention as amended, since the formula III compound

a. meets the specification requirement (e.g. that the formula III compound has a functional group suitable for conjugating with a nucleophile as described on present specification page 19) and is intended to be used as an "alkylating agent"and thus constitutes a "protected alkylating agent" within the scope of the presently claimed invention; and/or

b. the formula III compounds intended alkylating agent use is realized upon being reacted with a nucleophilic group upon being "deprotected" [e.g. placed in the presence of a disulfide containing compound (e.g. Metzger formula II compound) and/or a disulfide reducing agent (e.g. Zn in HCL/H2SO4)].

The Examiner lacks the facilities to make the necessary comparisons between prior art compounds and those compounds that may fall within the metes and bounds of the presently claimed invention. .

10. Claims 1, 14-16, 19, 21-30, 32, 33 and 37-44 are rejected under 35 U.S.C. 102(b) as being anticipated or in the alternative as being obvious over Van Atta et al. US Pat. No. 5,478,729 (12/95) alone or in view of the present specification to demonstrate inherency.

Initially, it is noted that the claims, as amended (e.g. see Amended claim 1) can be interpreted as **product-by -process** claims drawn to "an alkylating agent" made by reacting an "haloketone or alphahaloaldehyde" containing a functional group (e.g. a carbonyl) with a "protected functional group" (e.g. derivatized); the resulting protected functional group (e.g. a carbonyl protecting group) resulting in the claimed degree of activity when exposed to an an enzyme and a nucleophile or sulfhydryl group.

It is noted, that a product-by process claims are deemed by the PTO as product claims; wherein the process claim limitations are not afforded patentable weight.

Van Atta et al. disclose compositions, kits and assays for performing immunodetection of homocysteine in a sample. (E.g. see abstract; patent claims). The assays can be performed homogeneously or heterogeneously using solid supports (e.g. beads such as glass beads; see col. 5). Van Atta teaches the use of "modifying reagents" especially "alkylating agents" which are preferred and most preferentially the use of α-bromoacetylbenzoic acid (BABA) as the "protected alkylating agent" is specifically disclosed, exemplified and claimed (e.g. see col. 9, lines 20-25; patent claims 10, 25 etc.. It is noted that both BABA (e.g. example IV) and modified BABA (e.g. BABA-N-hydroxysuccinamide ester: see col. 21) constitute "protected alkylating agents" which appear to be within the scope of the presently claimed invention. It is further noted

that if a compound is clearly within the scope of the presently claimed invention; claimed functional characteristic must inherently flow therefrom (e.g. "deprotection" and reaction with a nucleophile). Additionally, both BABA and BABA-N-hydroxysuccinamide ester meet the specification requirement (e.g. has a functional group suitable for conjugating with a nucleophile as described on present specification page 19) and is intended to be used (and indeed is used) as an "alkylating agent"and thus constitutes a "protected alkylating agent" within the scope of the presently claimed invention; and/or both BABA and BABA-N-hydroxysuccinamide ester react with a nucleophilic group upon being "deprotected" [e.g. placed in the presence of a disulfide containing compound and/or disulfide reducing agent].

Further the reference BABA and BABA derivative compounds are analogous in structure to BABA and its derivatives disclosed in the present specification; and accordingly, the reference compounds would be expected to possess the newly claimed product-by-process claim limitation(s) e.g. be "an alkylating agent" made by reacting an "haloketone or alphahaloaldehyde" containing a functional group (e.g. a carbonyl) with a "protected functional group" (e.g. derivatized); the resulting protected functional group (e.g. a carbonyl protecting group) resulting in the claimed degree of activity when exposed to an an enzyme and a nucleophile or sulfhydryl group.

Additionally the patent discloses "releasing agents" particularly "disulfide reducing agents" with disclosed and exemplified phosphines being most preferred (e.g. see col. 15; Example IV and TCEP).

Accordingly, the reference clearly anticipates claims 1 and 14-16 which merely require a "protected alkylating agent alone or further combined with a "disulfide reducing agent" (e.g. TCEP).

With regard to present claims 32 and 33 which recite a homocysteine assay requiring a sample to be contacted with "a protected alkylating reagent" and a "ligand" that is capable of "specifically binding to a "modified homocysteine" to form an immunocomplex and further comprising a disulfide reducing agent; it is initially noted that if "ligand" is interpreted as being an antibody, the reference, as discussed above would anticipate claims 32 and 33. It is further noted that the reference specifically teaches the incorporation of a "ligand" as part of the "modifying agent" (e.g. see col. 14 bottom) which would alternatively anticipate this claim language.

To the extent that the presently claimed inventions are drawn to kits in which the individual components are separate or combined it is noted that the reference specifically is addressed to kits (E.g. see col. 20; patent claims 27-27). To the extent that the kit claims and/or methods further require the presence of an "activating agent capable of deprotecting to the protected alkylating agent" (e.g. alkaline phosphatase) it is noted that the patent reference teaches the use of "alkaline phosphatase" (e.g. Hcy-ABA-AP) in generating antibodies (e.g. see col. 21; and bottom of col. 22-top of col. 23) and thus would anticipate or render obvious the presence of alkaline phosphatase in kit form (e.g. claims 19, 26). With regard to the presence of "alkaline phosphatase" as part of the immunological assay per se it is noted that the use of "enzymes such as alkaline phosphatase" as a preferred "label" (e.g. see col. 5, lines 30-40) and the use of these

enzymes (e.g G-6Ph dehydrogenase) in the liquid assay (e.g. see bottom of col. 18-top of col. 19) would either anticipate or render obvious the incorporation of alkaline phosphatase in solution with the protecting alkylating agent, antibody etc. as found in the presently claimed invention. The use of microtiter well plates are disclosed (E.g. see col. 24, line 44).

Double Patenting

11. Claims 1, 14-16, 19, 21-30, 32, 33 and 37-44 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-29 of U.S. Patent No. 5,478,729 alone or, if necessary, in view of the present specification to demonstrate inherency.

Initially, it is noted that the claims, as amended (e.g. see Amended claim 1) can be interpreted as **product-by -process** claims drawn to "an alkylating agent" made by reacting an "haloketone or alphahaloaldehyde" containing a functional group (e.g. a carbonyl) with a "protected functional group" (e.g. derivatized); the resulting protected functional group (e.g. a carbonyl protecting group) resulting in the claimed degree of activity when exposed to an an enzyme and a nucleophile or sulfhydryl group.

It is noted, that a product-by process claims are deemed by the PTO as product claims; wherein the process claim limitations are not afforded patentable weight.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the patent claims disclose, compositions, kits and methods of use thereof comprising "modifying agents" particularly alkylating agents (e.g ketones substituted at alpha

position by halogens) , releasing agent (e.g. reducing agents), antibodies and labels which can be selected from 5 different types one of which are enzymes (e.g. see patent claim 13) in solution with or without supports. In this regard, BABA as being the ketone substituted at the alpha position by halogen; phosphines as disulfide reducing agents; and alkaline phosphatase for use in kits and assays are either disclosed or specifically exemplified as being preferred embodiments (e.g. see examples; bottom of col 15, col. 19 ; bottom of col. 20 to top of col. 21; col. 13, lines 25-30; col 5. Accordingly, the patent claim reference would render obvious the presently claimed invention.

Regarding the newly amended claim limitations describing a "protected alkylating agent" is noted that if a compound is clearly within the scope of the presently claimed invention; claimed functional characteristic must inherently flow therefrom (e.g. "deprotection" and subsequent reaction with a nucleophile). BABA meets the specification requirement for a "protected alkylating agent" (e.g. has a functional group suitable for conjugating with a nucleophile as described on present specification page 19) and is intended to be used (and indeed is used) as an "alkylating agent"and thus constitutes a "protected alkylating agent" within the scope of the presently claimed invention; and/or BABA reacts with a nucleophilic group upon being "deprotected" [e.g. placed in the presence of a disulfide containing compound and/or disulfide reducing agent].

Additionally the reference BABA and BABA derivative compounds are analogous in structure to BABA and its derivatives disclosed in the present specification; and accordingly, the

reference compounds would be expected to possess the newly claimed product-by-process claim limitation e.g. be "an alkylating agent" made by reacting an "haloketone or alphahaloaldehyde" containing a functional group (e.g. a carbonyl) with a "protected functional group" (e.g. derivatized); the resulting protected functional group (e.g. a carbonyl protecting group) resulting in the claimed degree of activity when exposed to an an enzyme and a nucleophile or sulfhydryl group.

General information regarding further correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Celsa whose telephone number is (703) 305-7556.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew J. Wang (art unit 1639), can be reached at (703)306-3217.

Any inquiry of a general nature, or relating to the status of this application, should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Bennett Celsa (art unit 1639)

December 17, 2002

BENNETT CELSA
PRIMARY EXAMINER